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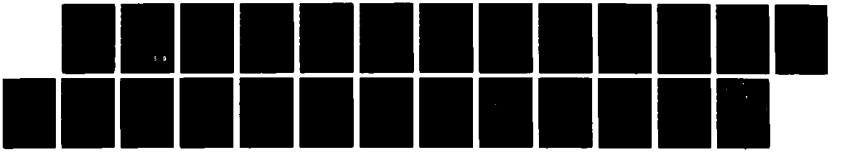

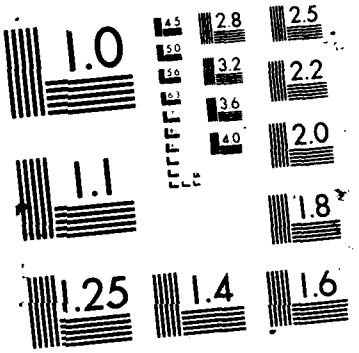
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Responses of Plasma Atrial Natriuretic Peptide to High Intensity Submaximal Exercise in the Heat

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Running Head: Plasma atrial natriuretic peptide and exercise in the heat

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SUMMARY

No data exists regarding human responses of atrial natriuretic peptide (ANP) to exercise in the heat. The purpose of this study was to examine the responses of plasma ANP to high intensity submaximal (71% ±0.9 $\dot{V}O_2$max) exercise in the heat over an eight day acclimation period. Fourteen healthy males volunteered to participate in the study. Subjects performed intermittent exercises on a treadmill (0% grade) during 50 min of each 100 min trial in an environmental chamber maintained at 41.2 ± 0.5°C, 39.0 ± 1.7% relative humidity. Blood was obtained from an antecubital vein after standing 20 min in the heat prior to exercise, and immediately after exercise was completed on days 1,4 and 8. ANP did not change pre- to post-exercise nor did it change over the eight day heat acclimation period despite other heat acclimation adaptations. Conversely, plasma aldosterone (ALDO),renin activity (PRA) and cortisol (COR) all increased ($p<0.05$) pre-to post-exercise on each day but again no changes were observed over the eight day period. These data support that ANP may not increase when ALDO and PRA increases.

Key Words: Atrial natriuretic peptide, cortisol, plasma renin activity, aldosterone, heat, males.

INTRODUCTION

The myriad of hormonal responses to exercise in the heat all consistently contribute to physiological mechanisms designed to conserve body fluid and electrolytes while maintaining normal cardiovascular function. Thus, exercise in a hot environment tends to cause increased release of antidiuretic hormone (ADH) and aldosterone (ALDO) along with increases in plasma renin activity (PRA) (Collins and Weiner, 1968).

The discovery of bioactive atrial peptides that influence fluid and electrolyte homeostasis was reported by deBold and colleagues in 1981 (deBold et al. 1981). Because the stimulus for release of atrial natriuretic peptide (ANP) appears to be atrial pressure or stretch, vasoconstriction or hypertension must be present (Schwartz et al. 1986). Therefore, it might be hypothesized that hormones that mediate or support the maintenance of adequate plasma volume or fullness of the blood stream such as PRA, angiotensin and ALDO or pressor agents such as epinephrine or norepinephrine or pituitary hormones such ADH as play a counter regulatory role (Genest and Cantin, 1986). Previous studies have indicated that ANP appears to inhibit the vasoconstrictor effects of norepinephrine and angiotensin II (Atlas et al. 1986; Genest and Cantin, 1986). Furthermore, it appears to inhibit the release of ADH and ALDO by acting on the pituitary and the adrenals (Atlas et al. 1986).

Unloading of stretch receptors would lead to diminished secretion and increased appearance of the storage form of ANP in cardiocyte granules. Whether it is a long

term regulator of plasma volume by modulating the effects of longer acting stimuli (e.g. ALDO) or plays a role in the defense of the heart from fatigue or failure seems debatable.

It might be also hypothesized that the rapid, massive and short diuresis due to ANP release appears consistent with more of an emergency safety valve role than a long term regulator (Blain, 1986). The possibility of a mechanistic role in heat-exhaustion and fatigue is particularly attractive. This is particularly true since an increase in cardiac output and stroke volume appear characteristic of the acclimatized individual, but a dramatic fall in cardiac output is characteristic of heat illness. A drop in cardiac output by atriopeptin II(APII) is always proportionally greater than the decrease in the mean arterial pressure under these conditions(Achermann et al. 1984, Gellaid et al. 1986). Total peripheral resistance tends to increase (Gellai et al. 1986) which could be helpful in supporting blood pressure in a system vasodilated peripherally by heat.

Both volume contraction and salt loss appear to increase cardiocyte granularity which is consistent with decreased release of ANP due to unloading of stretch receptors. This is consistent with a reduction in the "basal" release of the hormone (Schwartz et al. 1986).

Much of the research examining ANP has centered on pathological conditions in which fluid balance is disturbed as in hypertension and congestive heart failure (Atlas et al 1986; Burnett et al 1986). Very little information exists regarding the role of ANP in fluid balance in healthy humans. To our knowledge no studies exist which examine ANP responses to exercise in a hot environment. To elucidate any possible

role of ANP in the heat were measured plasma ANP, ALDO and PRA concentrations prior to and following high intensity submaximal exercise in the heat over an eight day heat acclimation period.

METHODS

Fourteen healthy male subjects volunteered to serve as subjects in this study. Subjects were medically screened and all gave written informed consent. None of the subjects were on medications during the study nor exhibited any contraindications to heat exposure and exercise. There physical characteristics were ($\bar{x}$ ± 1SD): age (yrs) 28.4 + 1.9, height (cm) 177.0 +2.0, weight (kg) 79.77+ 3.78, % body fat 18.7+1.4, maximal oxygen consumption (ml• kg•min^{-1}) 45.74 ± 1.96 and body surface area 1.96+0.50 (m^2). Subjects completed a health questionnaire, activity questionnaire, and history of heat exposure prior to initial testing. Data from these forms were examined to document that each subject was unacclimatized prior to the study.

One day prior to the eight day heat acclimation regime, each subject was given a progressive exercise test to determine maximum oxygen consumption ($\dot{V}O_2max$). $\dot{V}O_2max$ was used to calculate the relative exercise intensities of the exercise training. During both testing and training, a semi-automated system was used to collect and analyze expired gases. This system consisted of a Hewlett-Packard 85 B computer, scanner, and digital voltmeter which were interfaced with a gas meter (Parkinson-Cowan), oxygen analyzer (Applied Electrochemistry S3A) and carbon dioxide analyzer

(Beckman LB2). Rectal temperature (Tre) was monitored every four minutes using a rectal probe inserted 8 cm beyond the anal sphincter. Heart rate was continuously monitored using a Hewlett-Packard telemetry system.

The heat acclimation regime consisted of eight days of treadmill exercise (0% grade). Daily exposure consisted of 50 minutes of intermittent exercise during each 100 minute trial, in an environmental chamber maintained at 41.2 ± 0.5° C, 39.0 ± 1.7% relative humidity. Each subject performed all exercise sessions at the same time of day. Submaximal exercise testing protocols on days 1 and 8 were performed at the identical duration and intensity (71.8 ± 0.9% 9% $\dot{V}O_2$max). On day 4 the running exercise was performed at self paced intensity of 67.6 ± 2.3% $\dot{V}O_2$max which was not statistically different from the intensity used on days 1 and 8. The other days consisted of similar high intensity interval exercise. Water was drunk ad libitum throughout all trials, but could not be sprayed or poured on the body. Subjects were encouraged to drink adequate water both within and when away from the environmental chamber.

Upon arriving at the testing site each day, subjects were weighed and produced a urine sample which was analyzed for specific gravity. If any subject had a urine specific gravity greater than 1.030, he drank water until a more dilute urine was produced (specific gravity < 1.030).

A 20 minute equilibration period while standing in the heat preceded each antecubital blood sample (days 1, 4 and 8). A second standing antecubital blood sample was taken immediately post-exercise. The blood samples for measurement of

plasma cortisol (COR), plasma renin activity (PRA), and aldosterone (ALDO) were collected into chilled glass vacutainers containing the anticoagulant potassium EDTA (7.2 mg/5 ml whole blood). The blood was mixed gently, placed in ice and immediately centrifuged for fifteen minutes at 760 x g , 4° C after which the plasma was removed. Blood samples for measurement of ANP were collected into chilled glass vacutainers containing sodium heparin and 25 μl/ml whole blood of aprotinin (Sigma Chemical Co. St Louis, MO), gently mixed and centrifuged at 1500 x g, 4° C, after which the plasma was removed. Plasma samples were stored at -115° C until analyzed.

Hemoglobin was analyzed using the cyanmethemoglobin method (Hycel Inc., Houston, TX) and hematocrit was analyzed in triplicate using a micro-capillary technique. Duplicate serum sodium (Na^+) and potassium (K^+) levels were determined using a flame photometer (Rainin Instruments, FLM3). Changes in plasma volume (% Δ PV) were calculated from the changes in hematocrit and hemoglobin (Dill and Costill, 1974). Plasma osmolality was measured in duplicate using fresh unfrozen plasma with the freezing-point depression method (Precision Micro Osmette, Model 5004, Precision Systems).

Plasma COR and PRA immunoreactivity were quantitated in duplicate using commercially available radioimmunoassay test kits (New England Nuclear, North Billrica, MA). The formation of angiotensin I, indicative of PRA, was assessed at pH 6.0 and 37°C for 1 hour. Plasma ALDO immunoreactivity was determined using a commercially available radioimmunoassay test kit (Diagnostic Products Corporation, Los Angeles, CA). All of these assays were performed according to procedures and

methods outlined in the respective technical bulletins. Intra-assay variances for PRA, ALDO and COR, fell within manufactures suggested ranges and were 12.7%, 7.3% and 10% respectively. All duplicate samples demonstrated less than 3% differences. Triplicate sample measurements were made if the duplicates were greater than 5% difference.

We assayed for circulating concentrations of ANP in duplicate with the radioimmunoassay methods previously described in detail by Burnett et al. (1986). Commercially available ^{125}I ligand and antisera (Peninsula Laboratories, Belmont, CA) were used in the assay. Recovery from the extraction procedure was 83.5 ± 1.4 percent (mean and standard error) as determined by the addition of synthetic ANP to plasma. Interassay and intraassay variations were less than 3 and 4 percent respectively.

Determinations of the different plasma immunoreactivity (ir) values were accomplished with the use of a Beckman model 5500 Gamma counter and data reduction system.

Statistical evaluation of the data was accomplished by using a 3 x 2 ANOVA (days x pre/post). Subsequent post hoc analyses were performed using a Tukey test. Changes from day 1 to day 8 were evaluated using a two-tailed paired "t" test. Additionally, Pearson product-moment correlation coefficients were calculated for the data set. In this study, significance was chosen as $p < 0.05$.

RESULTS

All of the subjects were unacclimatized at the beginning of this investigation. No significant differences were found In mean entering body weight or mean entering urine specific gravity over the eight days. No significant differences were observed between the running intensities chosen on days I. 4 and 8.

The subjects showed the typical physiological effects characteristic of heat acclimation over the eight day period. The following variables all demonstrated significant decreases from day 1 to day 8; final exercise heart rate (170 ± 3 vs 144 ± 5 beats•min^{-1}).Δ heart rate (pre- to post-exercise) (84 ± 3 vs 68 ± 6 beats. min^{-1}). final Tre (39.17 ± 0.10 vs 38.52 ± 0.16^{o}C) and ΔTre (pre- to post-exercise)(2.04 ± 0.09 vs 1.46 ± 0.16^{o}C). Resting, pre-exercise plasma volume changes from day to day and plasma volume changes within days were calculated. Plasma volume significantly expanded (+5.9%) during the first four days of heat acclimation and stabilized through day 8 (+5.2%). There was also a significantly better defense of plasma volume during exercise on day 8 than on day 1 (- 5.1 ± 1.1 vs - 7.1 ± 0.9%).

No significant differences were found in serum sodium between days 1,4 or 8 for pre- or post-exercise values (day 1, pre=141 ± 1.0, post=140 ± 1.0; day 4, pre=141 ± 1.0, post=140 ± 1.0; day 8, pre=140 ± 1.0, post=141 ± 1.0 mmol/L). Serum potassium concentrations were significantly higher post-exercise on each of the three days, but no differences between days were observed (day 1, pre=4.3 ± 0.1, post=4.7 ± 0.1; day 4, pre=4.5 ± 0.1, post=4.7 ± 0.1; day 8, pre=4.4 ± 0. 1, post=4.8 ±

0.1mmol/L). Likewise, no significant differences were found in plasma osmolalities between days 1, 4 or 8 for pre or post exercise values (day 1, pre=288.9 ± 5.13, post=288.5 ± 4.5; day 4, pre=290.7 ± 4.42, post=291.0 ± 6.18; day 8, pre=287.57 ± 4.51, post=291.0 ± 6.02 mmol/kg).

A summary of plasma ANP responses to exercise in the heat over an eight day period appear in Figure 1. No significant differences were observed pre- to post-exercise, nor over the eight-day heat acclimation period.

Figures 2 and 3 depict the effects of exercise in the heat on circulating levels of ALDO and PRA. Increases were observed pre- to post-exercise on each day but no changes in resting or exercise responses were demonstrated over the eight day period.

In this study, plasma cortisol concentration was used as an indicator of ACTH release and heat stress. Figure 4 depicts the exercise responses of cortisol and indicates that cortisol increased pre- to post-exercise but did not change during over the eight-day heat acclimation period.

DISCUSSION

The primary aim of this study was to evaluate the plasma responses of ANP to high intensity submaximal exercise in the heat during an eight-day heat acclimation period. Comparisons of the physiological measurements demonstrated that typical acute heat acclimation adaptations had occurred in our subjects. (Armstrong and Dziados, 1986).

In this study no changes were observed in resting levels of ANP over the eight day acclimation period in spite of other acute physiological adaptations. This was consistent with the lack of any changes in other resting hormonal levels in this study. It is interesting to note that the resting plasma levels of ANP reported in this study appear about 30% less than previous levels for healthy subjects reported in another study (Burnett et al.1986) measured in a neutral environment. This finding is also consistent with data from our own laboratory for plasma levels of ANP measured in healthy subjects at rest in neutral temperatures (unpublished data). It is possible that elevation of plasma ALDO in response to intense heat during the 20 min of standing prior to exercise may partially account for the reduced levels observed in ANP(Kosunen et al.1976). This hypothesis is supported by (a) pre-exercise ALDO levels similar to previously reported resting heat exposure values (Kosunen et al. 1976; Francesconi et al. 1985; Kirby and Convertino, 1986) and (b) our statistical analysis indicating a significant inverse correlation between resting concentrations of ALDO and ANP ($r=-0.49$, $p<0.05$). It has been demonstrated that in the rat, cow and human adrenal tumor, ANP decreases ALDO synthesis (Atarashi et al.1984, Delean et al. 1984, Goodfriend et al. 1984, Kudo et al. 1984, Campbell et al. 1985). These findings suggest that ALDO increases after 20 min of intense heat exposure may in part influence ANP release. In addition, the depressed thyroid activity reported in response to heat exposure may also have contributed to the reduced ANP levels observed in this study (Collins and Weiner, 1986). It has recently been demonstrated that hypothyroidism is characterized by decreased plasma levels of ANP (Zimmerman et al. 1987).

The increase in ALDO and PRA pre- to post-exercise might be considered an important mechanism which contribute to support the maintenance of adequate plasma volume (Collins, 1968). Although ANP levels during submaximal exercise have not been previously described, one might predict that it might initially increase due to increased venous return to the heart causing atrial stretch. This effect, if it occurred at all, may have been quickly offset by a decreased venous return due to decreased plasma volume and peripheral vasodialation as core temperature rose. Pooling the blood in the periphery, especially the legs, during the 20 min equilibration period could have decreased venous return and partially explain the decreased ANP levels observed in the first sample.

Close examination of our individual subject data demonstrated that in one subject who demonstrated significant heat exhaustion symptoms at the end of an exercise trial had increased ANP levels 625% above basal levels compared to an 11% increase and a 190% decrease when heat symptoms were not present. This appears to indicate that ANP may in fact play a significant role in the defense of the heart from fatigue or failure under extreme physiological conditions (Blain, 1986). Further study of this possible mechanism needs to be specifically examined.

Our study appears to suggest that passive heat exposure and performance of exercise in the heat typically inhibits the physiological stimuli necessary to increase ANP release. Since the volume expansion was minimal (+5.2%) and there was no change in serum sodium, an adequate stimules for ANP release was apparently lacking. An apparent reduction in the "basal" release of the hormone is consistent

with a relative unloading of atrial stretch receptors due to peripheral vasodilation and the well-known tendency toward hypotension in the heat. Thus, physiological adjustments to heat may be partially related to ANP and counter regulation hormonal responses which we have previously hypothesized and discussed. Furthermore, these effects are not significantly altered despite significant heat acclimation changes. The possibility of both short and long term regulation remains possible but require further definitive study to describe specific mechanisms and the adaptive time course.

ACKNOWLEDGEMENTS

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DISCLAIMERS

Human subjects participated in these studies after giving their free and informed voluntary consent. Investigators adhered to AR 70-25 and USAMRDC Regulation 70-25 on Use of Volunteers in Research.

The views, opinions, and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other official documentation.

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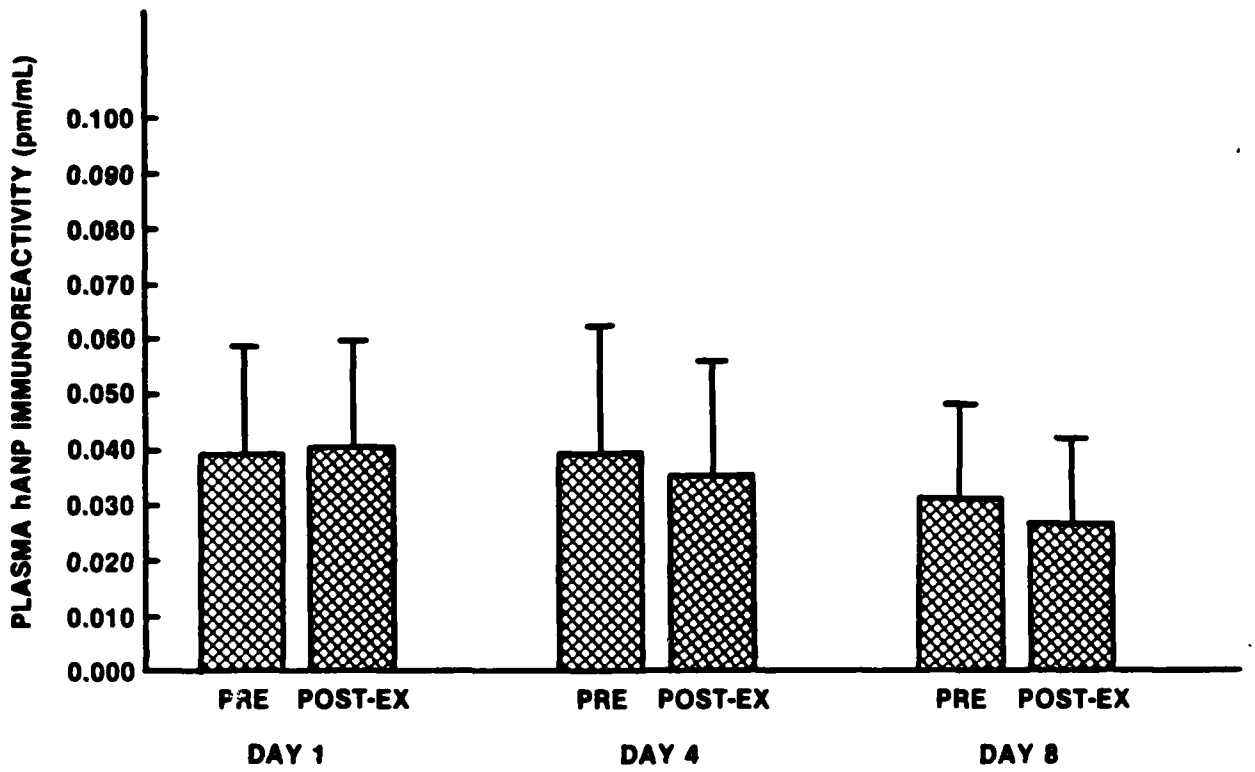
FIGURE LEGE''DS

Figure 1. Plasma human atrial natriuretic peptide (hANP) responses before and after high intensity exercise in the heat over an eight day period. Values shown are means and ± 1SD.

Figure 2. Plasma aldosterone immunoractivity responses before and after high intensity exercise in the heat over an eight day period. Values shown are means and ± 1SD. *=$p<0.0^{r}$ versus corresponding pre-exercise value.

Figure 3. Plasma renin immunoractivity responses before and after high intensity exercise in the heat over an eight day period. Values shown are means and ± 1SD. *=$p<0.05$ versus corresponding pre-exercise value.

Figure 4. Plasma cortisol immunoractivity (ir) responses before and after high intensity exercise in the heat over an eight day period. Values shown are means and ± 1SD. Δ=$p<0.05$ versus corresponding pre-exericse value.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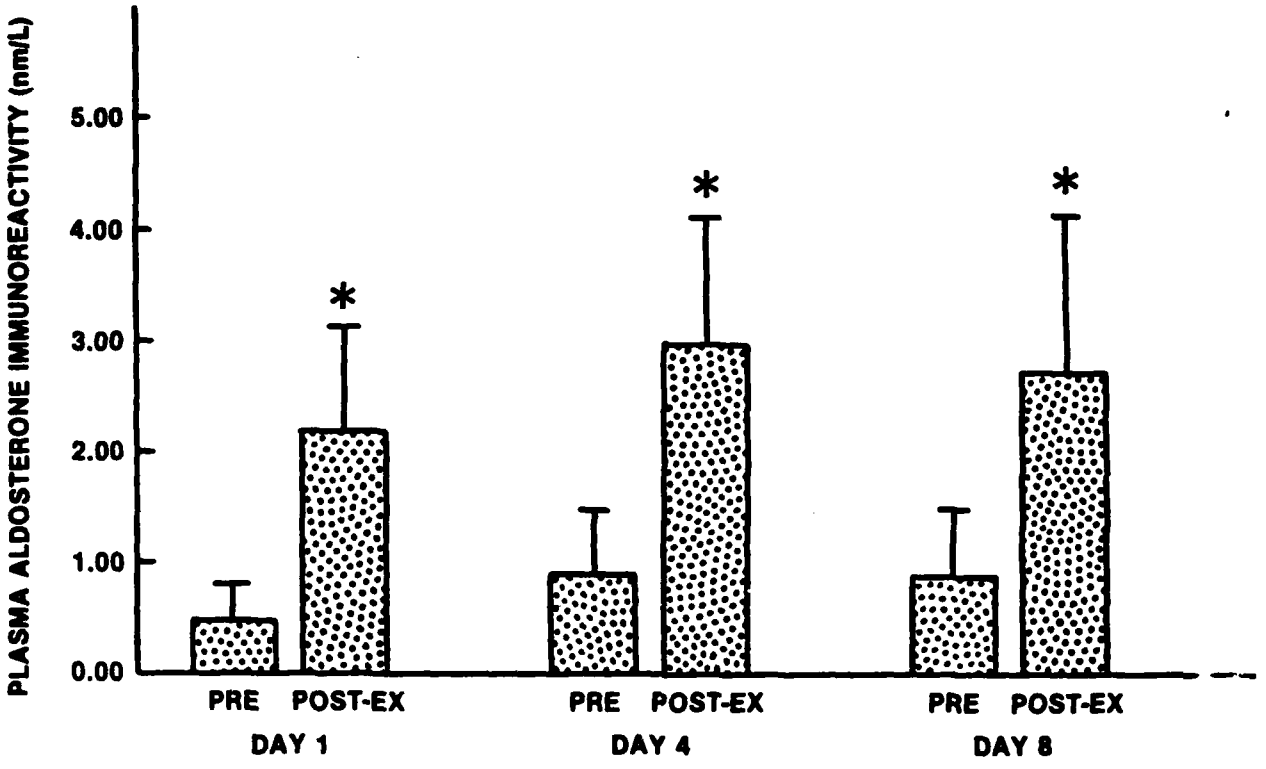
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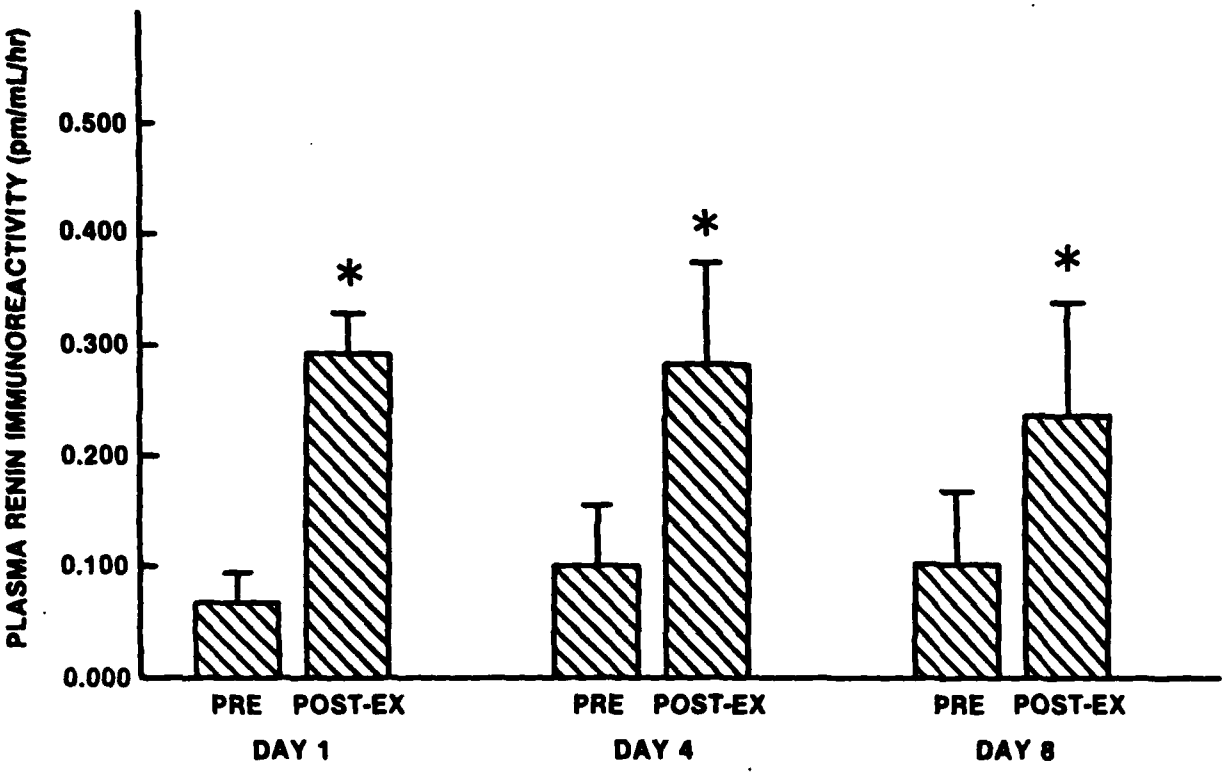
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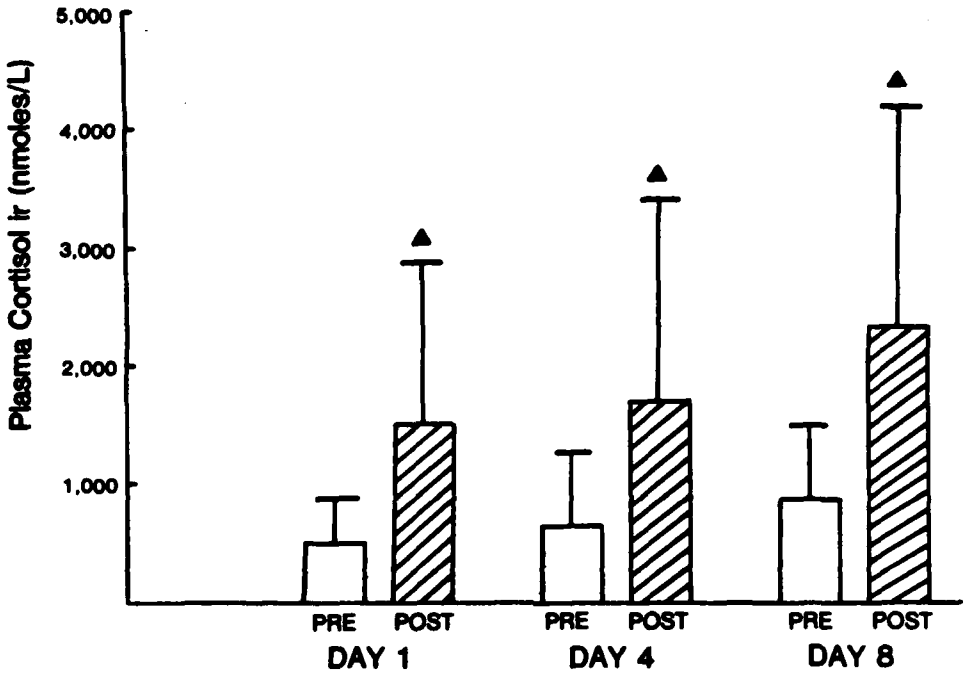
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